Renal Injury Due To Environmental Toxins, Drugs, and Contrast Agents

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The kidneys are susceptible to toxic or ischemic injury for several reasons. Thus, it is not surprising that an impressive list of exogenous drugs and chemicals can cause clinical acute renal failure (ARF) [1]. On the contrary, the contribution of environmental toxins to ARF is rather limited. In this chapter, some of the most common drugs and exogenous toxins encountered by the nephrologist in clinical practice are discussed in detail.

The clinical expression of the nephrotoxicity of drugs and chemicals is highly variable and is influenced by several factors. Among these is the direct toxic effect of drugs and chemicals on a particular type of nephron cell, the pharmacologic activity of some substances and their effects on renal function, the high metabolic activity (*ie*, vulnerability) of particular segments of the nephron, the multiple transport systems, which can result in intracellular accumulation of drugs and chemicals, and the high intratubule concentrations with possible precipitation and crystallization of particular drugs.

CHAPTER

11

General Nephrotoxic Factors

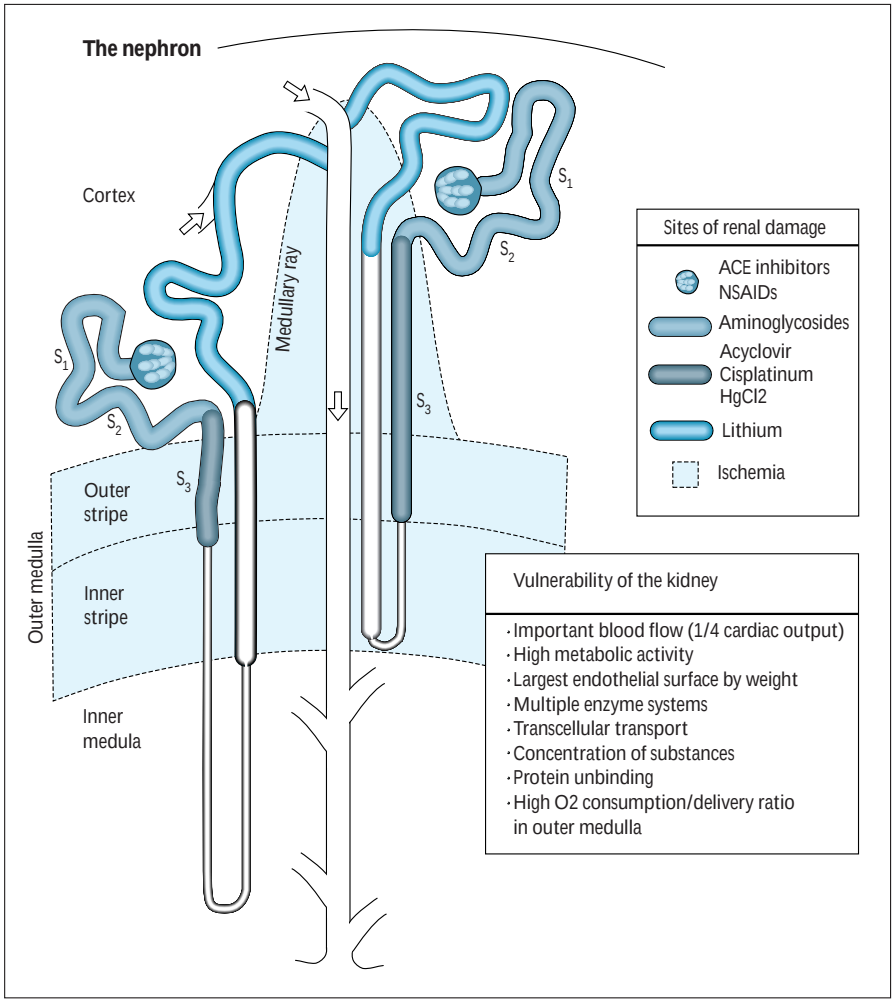

FIGURE 11-1

Sites of renal damage, including factors that contribute to the kidney's susceptibility to damage. ACE—angiotensin-converting enzyme; NSAID—nonsteroidal anti-inflammatory drugs; $HgCl_2$—mercuric chloride.

DRUGS AND CHEMICALS ASSOCIATED WITH ACUTE RENAL FAILURE

Mechanisms

M1 Reduction in renal perfusion through alteration of intrarenal hemodynamics
M2 Direct tubular toxicity
M3 Heme pigment–induced toxicity (rhabdomyolysis)
M4 Intratubular obstruction by precipitation of the agents or its metabolites or byproducts
M5 Allergic interstitial nephritis
M6 Hemolytic-uremic syndrome

M1	M2	M3	M4	M5*	M6	Drugs
✓	✓				✓	Cyclosporine, tacrolimus
✓	✓					Amphotericin B, radiocontrast agents
✓				✓		Nonsteroidal anti-inflammatory drugs
✓						Angiotensin-converting enzyme inhibitors, interleukin-2†
✓	✓		✓			Methotrexate§
	✓					Aminoglycosides, cisplatin, foscarnet, heavy metals, intravenous immunoglobulin¶, organic solvents, pentamidine
		✓			✓	Cocaine
		✓				Ethanol, lovastatin**
			✓	✓		Sulfonamides
			✓			Acyclovir, Indinavir, chemotherapeutic agents, ethylene glycol***
				✓		Allopurinol, cephalosporins, cimetidine, ciprofloxacin, furosemide, penicillins, phenytoin, rifampin, thiazide diuretics
					✓	Conjugated estrogens, mitomycin, quinine

* Many other drugs in addition to the ones listed can cause renal failure by this mechanism.
† Interleukin-2 produces a capillary leak syndrome with volume contractions.
§ Uric acid crystals form as a result of tumor lysis.
¶ The mechanism of this agent is unclear but may be due to additives.
** Acute renal failure is most likely to occur when lovastatin is given in combination with cyclosporine.
*** Ethylene glycol–induced toxicity can cause calcium oxalate crystals.

FIGURE 11-2
Drugs and chemicals associated with acute renal failure. (*Apapted from* Thadhani, *et al.* [2].)

Aminoglycosides

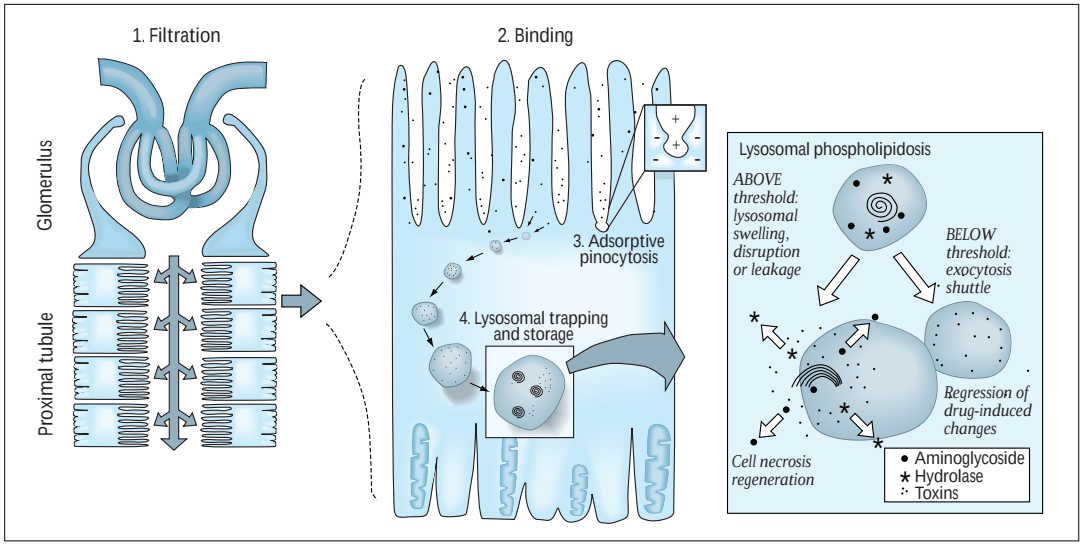

FIGURE 11-3

Renal handling of aminoglycosides: 1) glomerular filtration; 2) binding to the brush border membranes of the proximal tubule; 3) pinocytosis; and 4) storage in the lysosomes [3].

Nephrotoxicity and otovestibular toxicity remain frequent side effects that seriously limit the use of aminoglycosides, a still important class of antibiotics. Aminoglycosides are highly charged, polycationic, hydrophilic drugs that cross biologic membranes little, if at all [4,5]. They are not metabolized but are eliminated unchanged almost entirely by the kidneys. Aminoglycosides are filtered by the glomerulus at a rate almost equal to that of water. After entering the luminal fluid of proximal renal tubule, a small but toxicologically important portion of the filtered drug is reabsorbed and stored in the proximal tubule cells. The major transport of aminoglycosides into proximal tubule cells involves interaction with acidic, negatively charged phospholipid-binding sites at the level of the brush border membrane.

After charge-mediated binding, the drug is taken up into the cell in small invaginations of the cell membrane, a process in which megalin seems to play a role [6]. Within 1 hour of injection, the drug is located at the apical cytoplasmic vacuoles, called endocytotic vesicles. These vesicles fuse with lysosomes, sequestering the unchanged aminoglycosides inside those organelles.

Once trapped in the lysosomes of proximal tubule cells, aminoglycosides electrostatically attached to anionic membrane phospholipids interfere with the normal action of some enzymes (*ie*, phospholipases and sphingomyelinase). In parallel with enzyme inhibition, undigested phospholipids originating from the turnover of cell membranes accumulate in lysosomes, where they are normally digested. The overall result is lysosomal phospholipidosis due to nonspecific accumulation of polar phospholipids as "myeloid bodies," so called for their typical electron microscopic appearance. (*Adapted from* De Broe [3].)

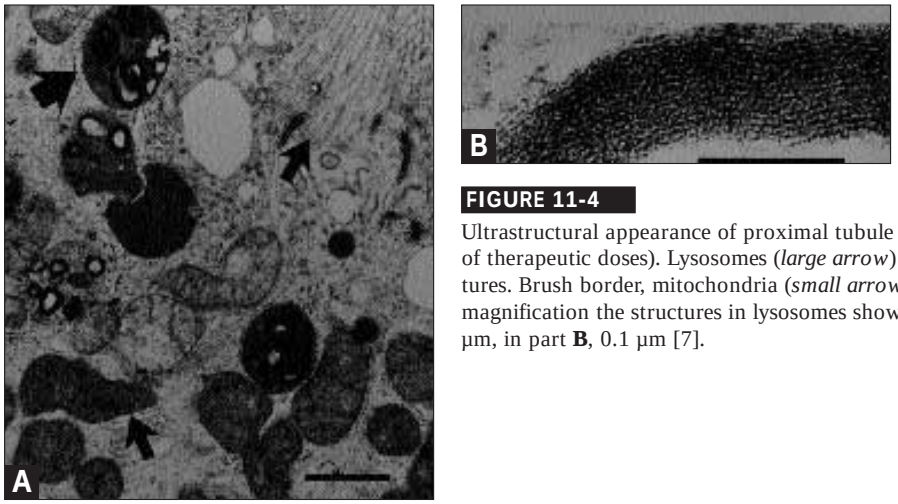

FIGURE 11-4

Ultrastructural appearance of proximal tubule cells in aminoglycoside-treated patients (4 days of therapeutic doses). Lysosomes (*large arrow*) contain dense lamellar and concentric structures. Brush border, mitochondria (*small arrows*) and peroxisomes are unaltered. At higher magnification the structures in lysosomes show a periodic pattern. The bar in **A** represents 1 µm, in part **B**, 0.1 µm [7].

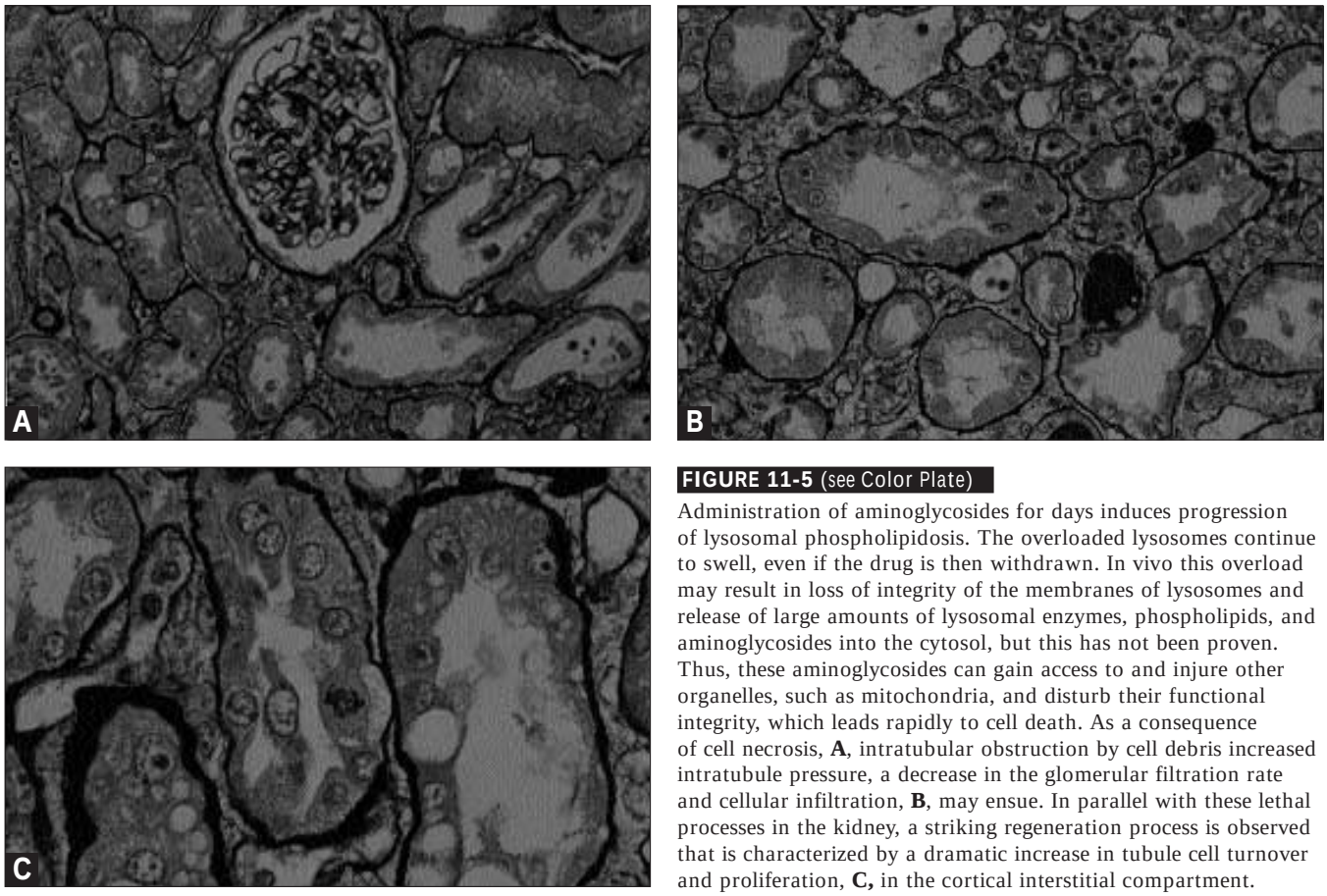

FIGURE 11-5 (see Color Plate)

Administration of aminoglycosides for days induces progression of lysosomal phospholipidosis. The overloaded lysosomes continue to swell, even if the drug is then withdrawn. In vivo this overload may result in loss of integrity of the membranes of lysosomes and release of large amounts of lysosomal enzymes, phospholipids, and aminoglycosides into the cytosol, but this has not been proven. Thus, these aminoglycosides can gain access to and injure other organelles, such as mitochondria, and disturb their functional integrity, which leads rapidly to cell death. As a consequence of cell necrosis, **A**, intratubular obstruction by cell debris increased intratubule pressure, a decrease in the glomerular filtration rate and cellular infiltration, **B**, may ensue. In parallel with these lethal processes in the kidney, a striking regeneration process is observed that is characterized by a dramatic increase in tubule cell turnover and proliferation, **C,** in the cortical interstitial compartment.

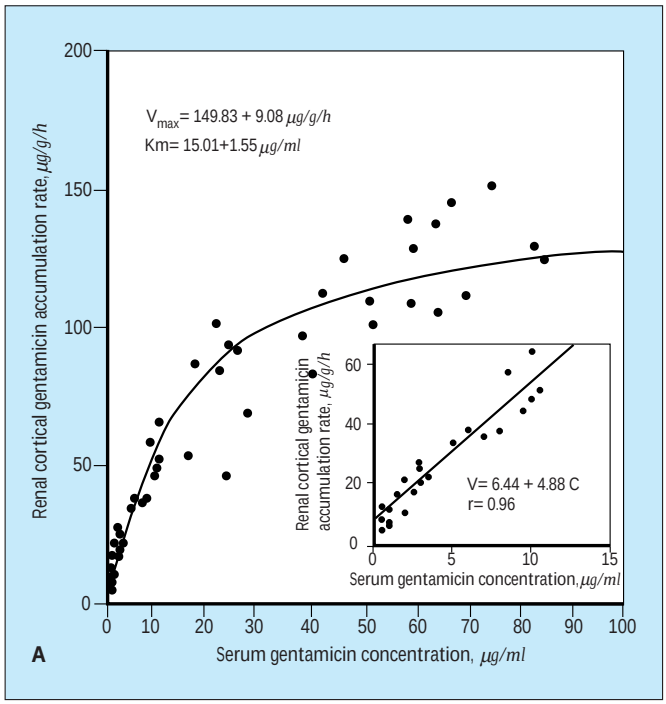

FIGURE 11-6

A, Relationship between constant serum levels and concomitant renal cortical accumulation of gentamicin after a 6 hour intravenous infusion in rats. The rate of accumulation is expressed in micrograms of aminoglycoside per gram of wet kidney cortex per hour, due to the linear accumulation in function of time. Each point represents one rat whose aminoglycosides were measured in both kidneys at the end of the infusion and the serum levels assayed twice during the infusion [8].

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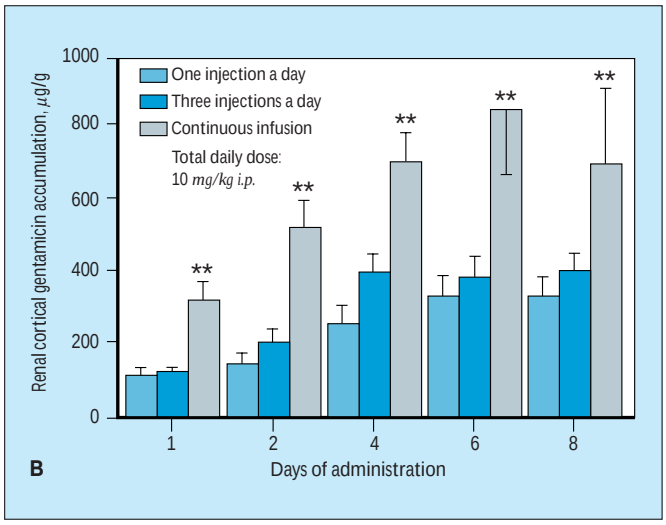
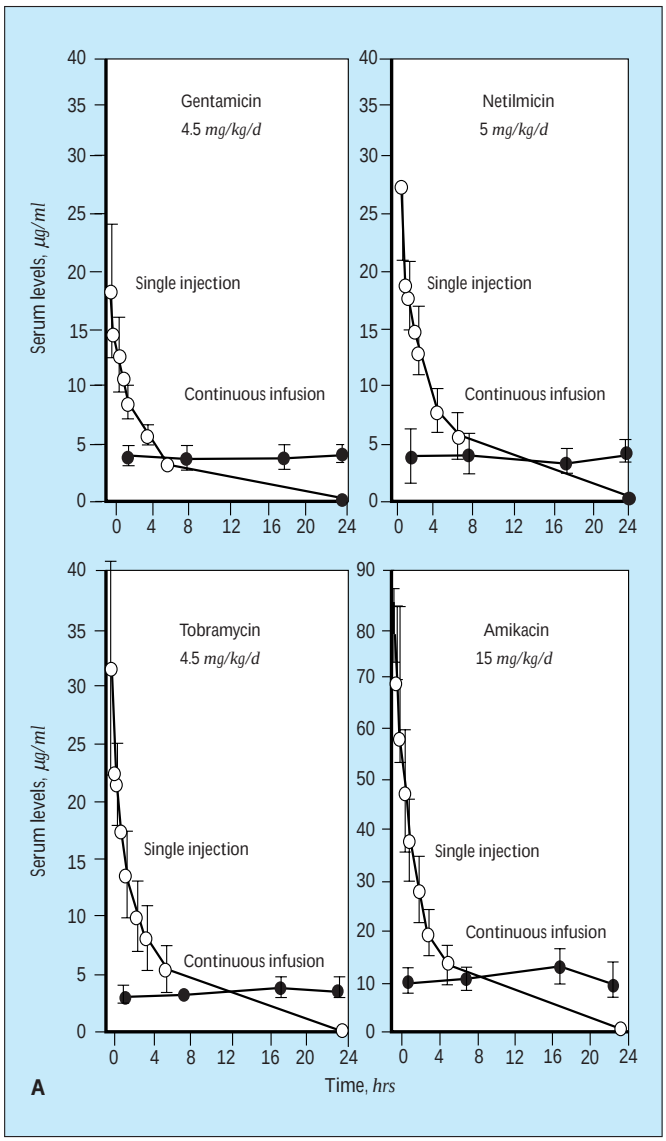


FIGURE 11-6 *(Continued)*

B, Kidney cortical concentrations of gentamicin in rats given equal daily amounts of aminoglycoside in single injections, three injections, or by continuous infusion over 8 days. Each block represents the mean of seven rats ±SD. Significance is shown only between cortical levels achieved after continuous infusion and single injections (asterisk—$P < 0.05$; double asterisk—$P < 0.01$) [9].

In rats, nephrotoxicity of gentamicin is more pronounced when the total daily dose is administered by continuous infusion rather than as a single injection. Thus, a given daily drug does not produce the same degree of toxicity when it is given by different routes. Indeed, renal cortical uptake is "less efficient" at high serum concentration than at low ones. A single injection results in high peak serum levels that overcome the saturation limits of the renal uptake mechanism. The high plasma concentrations are followed by fast elimination and, finally, absence of the drug for a while. This contrasts with the continuous low serum levels obtained with more frequent dosing when the uptake at the level of the renal cortex is not only more efficient but remains available throughout the treatment period. V_{max}—maximum velocity.



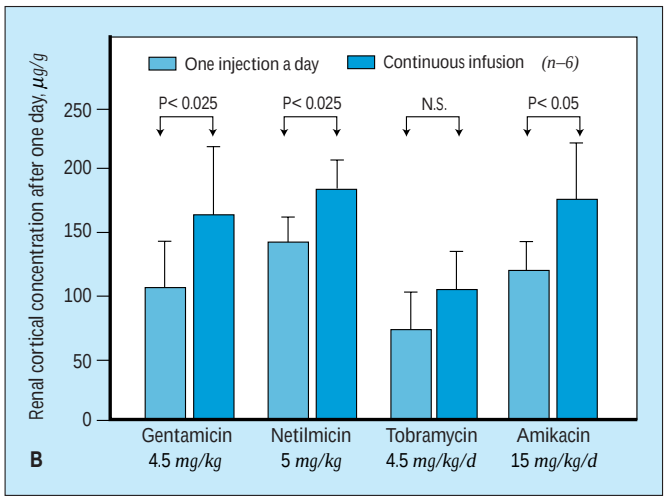


FIGURE 11-7

Course of serum concentrations, **A**, and of renal cortical concentrations, **B**, of gentamicin, netilmicin, tobramycin, and amikacin after dosing by a 30-minute intravenous injection or continuous infusion over 24 hours [10,11].

Two trials in humans found that the dosage schedule had a critical effect on renal uptake of gentamicin, netilmicin [10], amikacin, and tobramycin [11]. Subjects were patients with normal renal function (serum creatinine concentration between 0.9 and 1.2 mg/dL, proteinuria lower than 300 mg/24 h) who had renal cancer and submitted to nephrectomy. Before surgery, patients received gentamicin (4.5 mg/kg/d), netilmicin (5 mg/kg/d), amikacin (15 mg/kg/d), or tobramycin (4.5 mg/kg/d) as a single injection or as a continuous intravenous infusion over 24 hours. The single-injection schedule resulted in 30% to 50% lower cortical drug concentrations of netilmicin, gentamicin, and amikacin as compared with continuous infusion. For tobramycin, no difference in renal accumulation could be found, indicating the linear cortical uptake of this particular aminoglycoside [8]. These data, which supported decreased nephrotoxic potential of single-dose regimens, coincided with new insights in the antibacterial action of aminoglycosides (concentration-dependent killing of gram-negative bacteria and prolonged postantibiotic effect) [12]. N.S.—not significant.

RISK FACTORS FOR AMINOGLYCOSIDE NEPHROTOXICITY

Patient-Related Factors	Aminoglycoside-Related Factors	Other Drugs
Older age*	Recent aminoglycoside therapy	Amphotericin B
Preexisting renal disease		Cephalosporins
Female gender	Larger doses*	Cisplatin
Magnesium, potassium, or calcium deficiency*	Treatment for 3 days or more*	Clindamycin
Intravascular volume depletion*		Cyclosporine
Hypotension*	Dose regimen*	Foscarnet
Hepatorenal syndrome		Furosemide
Sepsis syndrome		Piperacillin
		Radiocontrast agents
		Thyroid hormone

* Similar to experimental data.

FIGURE 11-8

Risk factors for aminoglycoside nephrotoxicity. Several risk factors have been identified and classified as patient related, aminoglycoside related, or related to concurrent administration of certain drugs.

The usual recommended aminoglycoside dose may be excessive for older patients because of decreased renal function and decreased regenerative capacity of a damaged kidney. Preexisting renal disease clearly can expose patients to inadvertent overdosing if careful dose adjustment is not performed. Hypomagnesemia, hypokalemia, and calcium deficiency may be predisposing risk factors for consequences of aminoglycoside-induced damage [13]. Liver disease is an important clinical risk factor for aminoglycoside nephrotoxicity, particularly in patients with cholestasis [13]. Acute or chronic endotoxemia amplifies the nephrotoxic potential of the aminoglycosides [14].

PREVENTION OF AMINOGLYCOSIDE NEPHROTOXICITY

- Identify risk factor
  - Patient related
  - Drug related
  - Other drugs
- Give single daily dose of gentamicin, netilmicin, or amikacin
- Reduce the treatment course as much as possible
- Avoid giving nephrotoxic drugs concurrently
- Make interval between aminoglycoside courses as long as possible
- Calculate glomerular filtration rate out of serum creatinine concentration

FIGURE 11-9

Prevention of aminoglycoside nephrotoxicity. Coadministration of other potentially nephrotoxic drugs enhances or accelerates the nephrotoxicity of aminoglycosides. Comprehension of the pharmacokinetics and renal cell biologic effects of aminoglycosides, allows identification of aminoglycoside-related nephrotoxicity risk factors and makes possible secondary prevention of this important clinical nephrotoxicity.

Amphotericin B

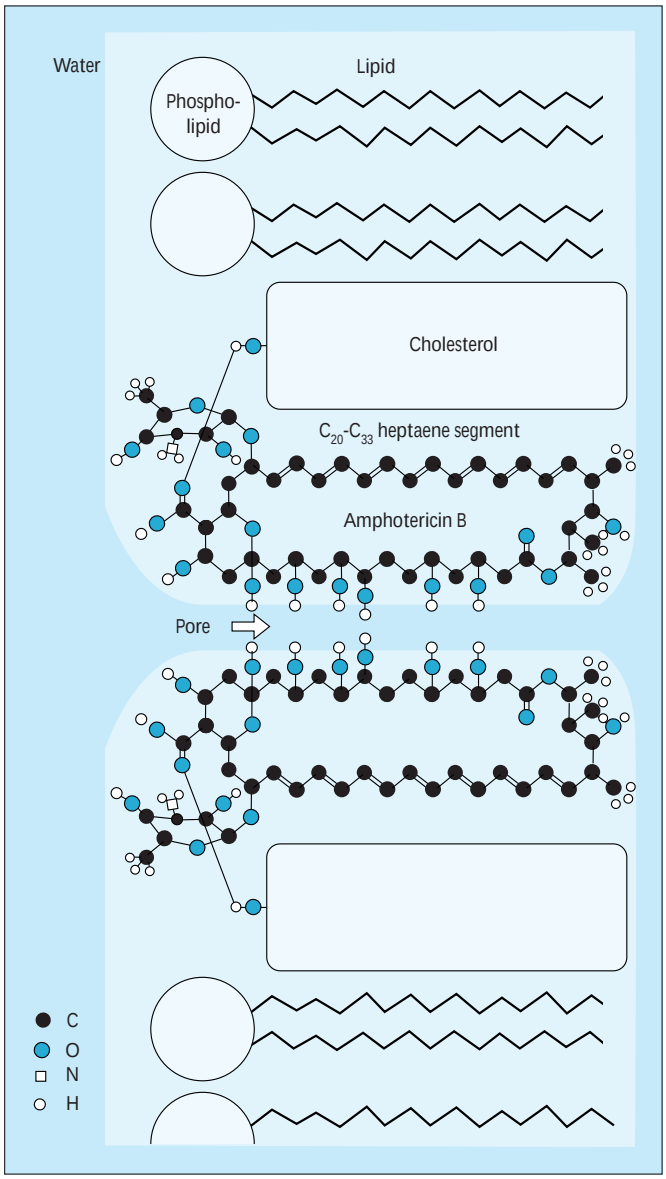


FIGURE 11-10

Proposed partial model for the amphotericin B (AmB)–induced pore in the cell membrane. AmB is an amphipathic molecule: its structure enhances the drug's binding to sterols in the cell membranes and induces formation of aqueous pores that result in weakening of barrier function and loss of protons and cations from the cell. The drug acts as a counterfeit phospholipid, with the C_{15} hydroxyl, C_{16} carboxyl, and C_{19} mycosamine groups situated at the membrane-water interface, and the C_1 to C_{14} and C_{20} to C_{33} chains aligned in parallel within the membrane. The heptaene chain seeks a hydrophobic environment, and the hydroxyl groups seek a hydrophilic environment. Thus, a cylindrical pore is formed, the inner wall of which consists of the hydroxyl-substituted carbon chains of the AmB molecules and the outer wall of which is formed by the heptaene chains of the molecules and by sterol nuclei [15].

RISK FACTORS IN THE DEVELOPMENT OF AMPHOTERICIN NEPHROTOXICITY

Age
Concurrent use of diuretics
Abnormal baseline renal function
Larger daily doses
Hypokalemia
Hypomagnesemia
Other nephrotoxic drugs (aminoglycosides, cyclosporine)

FIGURE 11-11

Risk factors for development of amphotericin B (AmB) nephrotoxicity. Nephrotoxicity of AmB is a major problem associated with clinical use of this important drug. Disturbances in both glomerular and tubule function are well described. The nephrotoxic effect of AmB is initially a distal tubule phenomenon, characterized by a loss of urine concentration, distal renal tubule acidosis, and wasting of potassium and magnesium, but it also causes renal vasoconstriction leading to renal ischemia. Initially, the drug binds to membrane sterols in the renal vasculature and epithelial cells, altering its membrane permeability. AmB-induced vasoconstriction and ischemia to very vulnerable sections of the nephron, such as medullary thick ascending limb, enhance the cell death produced by direct toxic action of AmB on those cells. This explains the salutary effect on AmB nephrotoxicity of salt loading, furosemide, theophylline, or calcium channel blockers, all of which improve renal blood flow or inhibit transport in the medullary thick ascending limb.

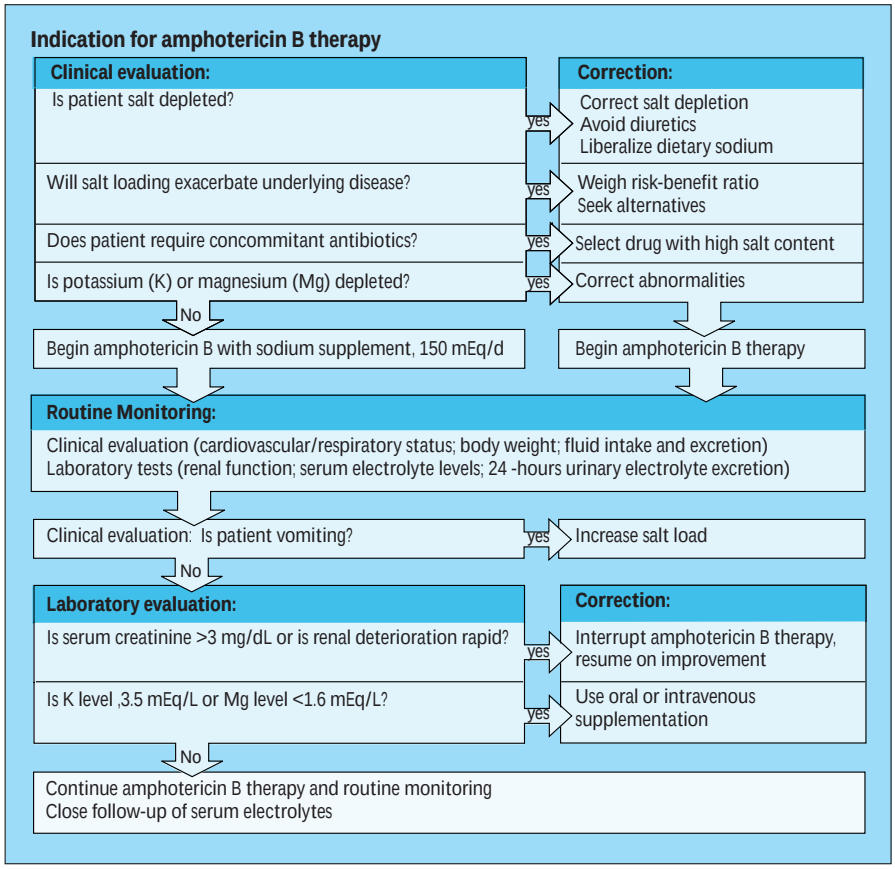


FIGURE 11-12

Proposed approach for management of amphotericin B (AmB) therapy. Several new formulations of amphotericin have been developed either by incorporating amphotericin into liposomes or by forming complexes to phospholipid. In early studies, nephrotoxicity was reduced, allowing an increase of the cumulative dose. Few studies have established a therapeutic index between antifungal and nephrotoxic effects of amphotericin. To date, the only clinically proven intervention that reduces the incidence and severity of nephrotoxicity is salt supplementation, which should probably be given prophylactically to all patients who can tolerate it. (*From* Bernardo JF, *et al.* [16]; with permission.)

Cyclosporine

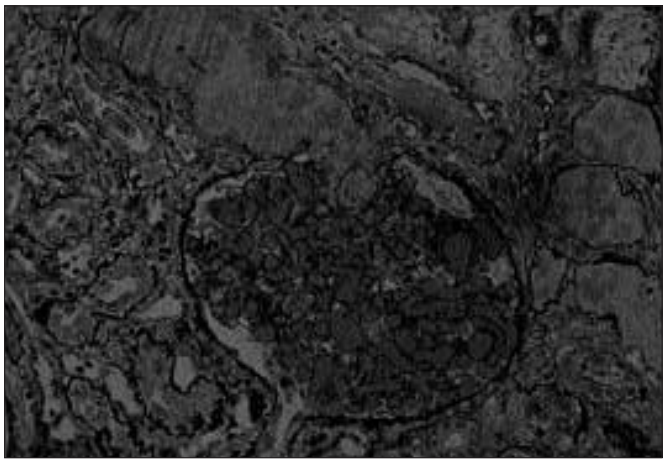


FIGURE 11-13 (see Color Plate)
Intravascular coagulation in a cyclosporine-treated renal transplant recipient. Cyclosporine produces a dose-related decrease in renal function in experimental animals and humans [17] that is attributed to the drug's hemodynamic action to produce vasoconstriction of the afferent arteriole entering the glomerulus. When severe enough, this can decrease glomerular filtration rate. Although the precise pathogenesis of the renal hemodynamic effects of cyclosporine are unclear, endothelin, inhibition of nitric oxide, release of vasoconstrictor prostaglandins such as thromboxane A_2, and activation of the sympathetic nervous system, are among the candidates for cyclosporine-induced vasoconstriction [18].

The diagnosis of cyclosporine-induced acute renal dysfunction is not difficult when the patient has no other reason for reduced renal function (*eg*, psoriasis, rheumatoid arthritis). In renal transplant recipients, however, the situation is completely different. In this clinical setting, the clinician must differentiate between cyclosporine injury and acute rejection. The incidence of this acute cyclosporine renal injury can be enhanced by extended graft preservation, preexisting histologic lesions, donor hypotension, or preoperative complications. The gold standard for this important distinction remains renal biopsy.

In addition, cyclosporine has been associated with hemolytic-uremic syndrome with thrombocytopenia, red blood cell fragmentation, and intravascular (intraglomerular) coagulation. Again, this drug-related intravascular coagulation has to be differentiated from that of acute rejection. The absence of clinical signs and of rejection-related interstitial edema and cellular infiltrates can be helpful.

Vanrenterghem and coworkers [19] found a high incidence of venous thromboembolism shortly after (several of them within days) cadaveric kidney transplantation in patients treated with cyclosporine, in contrast to those treated with azathioprine. Recent studies [20] have shown that impaired fibrinolysis, due mainly to excess plasminogen activator inhibitor (PAI-1), may also contribute to this imbalance in coagulation and anticoagulation during cyclosporine treatment.

Lithium-Induced Acute Renal Failure

SIGNS AND SYMPTOMS OF TOXIC EFFECTS OF LITHIUM

Toxic Effect	Plasma Lithium Level	Signs and Symptoms
Mild	1–1.5 mmol/L	Impaired concentration, lethargy, irritability, muscle weakness, tremor, slurred speech, nausea
Moderate	1.6–2.5 mmol/L	Disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dysarthria, muscle fasciculation, vomiting
Severe	>2.5 mmol/L	Impaired consciousness (with progression to coma), delirium, ataxia, generalized fasciculations, extrapyramidal symptoms, convulsions, impaired renal function

FIGURE 11-14
Symptoms and signs of toxic effects of lithium. Lithium can cause acute functional and histologic (usually reversible) renal injury. Within 24 hours of administration of lithium to humans or animals, sodium diuresis occurs and impairment in the renal concentrating capacity becomes apparent. The defective concentrating capacity is caused by vasopressin-resistant (exogenous and endogenous) diabetes insipidus. This is in part related to lithium's inhibition of adenylate cyclase and impairment of vasopressin-induced generation of cyclic adenosine monophosphatase.

Lithium-induced impairment of distal urinary acidification has also been defined.

Acute lithium intoxication in humans and animals can cause acute renal failure. The clinical picture features nonspecific signs of degenerative changes and necrosis of tubule cells [21]. The most distinctive and specific acute lesions lie at the level of the distal tubule [22]. They consist of swelling and vacuolization of the cytoplasm of the distal nephron cells plus periodic acid-Schiff–positive granular material in the cytoplasm (shown to be glycogen) [23]. Most patients receiving lithium have side effects, reflecting the drug's narrow therapeutic index.

DRUG INTERACTIONS WITH LITHIUM

Salt depletion strongly impairs renal elimination of lithium.
Salt loading increases absolute and fractional lithium clearance.

Diuretics	
Acetazolamide	Increased lithium clearance
Thiazides	Increased plasma lithium level due to decreased lithium clearance
Loop diuretics	Acute increased lithium clearance
Amiloride	Usually no change in plasma lithium level; may be used to treat lithium-induced polyuria
Nonsteroidal anti-inflammatory drugs	Increased plasma lithium level due to decreased renal lithium clearance (exceptions are aspirin and sulindac)
Bronchodilators (aminophylline, theophylline)	Decreased plasma lithium level due to increased renal lithium clearance
Angiotensin-converting enzyme inhibitors	May increase plasma lithium level
Cyclosporine	Decreased lithium clearance

FIGURE 11-15

Drug interactions with lithium [24]. Acute renal failure, with or without oliguria, can be associated with lithium treatment, and with severe dehydration. In this case, acute renal failure can be considered a prerenal type; consequently, it resolves rapidly with appropriate fluid therapy. Indeed, the histologic appearance in such cases is remarkable for its lack of significant abnormalities. Conditions that stimulate sodium retention and consequently lithium reabsorption, such as low salt intake and loss of body fluid by way of vomiting, diarrhea, or diuretics, decreasing lithium clearance should be avoided. With any acute illness, particularly one associated with gastrointestinal symptoms such as diarrhea, lithium blood levels should be closely monitored and the dose adjusted when necessary. Indeed, most episodes of acute lithium intoxication are largely predictable, and thus avoidable, provided that precautions are taken [25].

Removing lithium from the body as soon as possible the is the mainstay of treating lithium intoxication. With preserved renal function, excretion can be increased by use of furosemide, up to 40 mg/h, obviously under close monitoring for excessive losses of sodium and water induced by this loop diuretic. When renal function is impaired in association with severe toxicity, extracorporeal extraction is the most efficient way to decrease serum lithium levels. One should, however, remember that lithium leaves the cells slowly and that plasma levels rebound after hemodialysis is stopped, so that longer dialysis treatment or treatment at more frequent intervals is required.

Inhibitors of the Renin-Angiotensin System

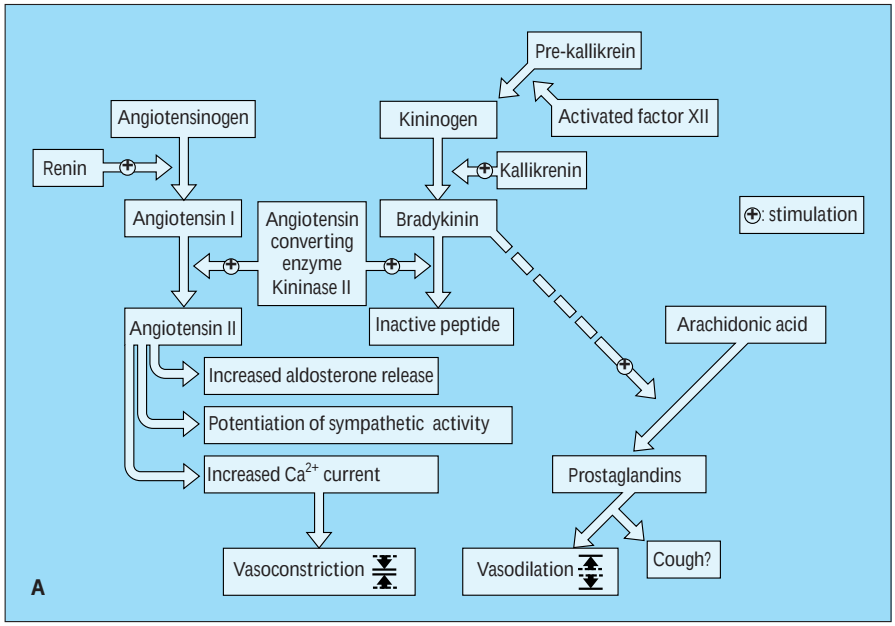


FIGURE 11-16

Soon after the release of this useful class of antihypertensive drugs, the syndrome of functional acute renal insufficiency was described as a class effect. This phenomenon was first observed in patients with renal artery stenosis, particularly when the entire renal mass was affected, as in bilateral renal artery stenosis or in renal transplants with stenosis to a solitary kidney [26]. Acute renal dysfunction appears to be related to loss of postglomerular efferent arteriolar vascular tone and in general is reversible after withdrawing the angiotensin-converting enzyme (ACE) inhibitor [27].

Inhibition of the ACE kinase II results in at least two important effects: depletion of angiotensin II and accumulation of bradykinin [28]. The role of the latter effect on renal perfusion pressure is not clear, **A**.

To understand the angiotensin I converting enzyme inhibitor–induced drop in glomerular filtration rate, it is important to understand the physiologic role of the renin-angiotensin system in the regulation of renal hemodynamics, **B**. When renal perfusion drops, renin is released into the plasma and lymph by the juxtaglomerular cells of the kidneys. Renin cleaves angiotensinogen to form angiotensin I, which is cleaved further by converting enzyme to form angiotensin II, the principal effector molecule in this system. Angiotensin II participates in glomerular filtration rate regulation in a least two ways. First, angiotensin II increases arterial pressure—directly and acutely by causing vasoconstriction and more "chronically" by increasing body fluid volumes through stimulation of renal sodium retention; directly through an effect on the tubules, as well as by stimulating thirst

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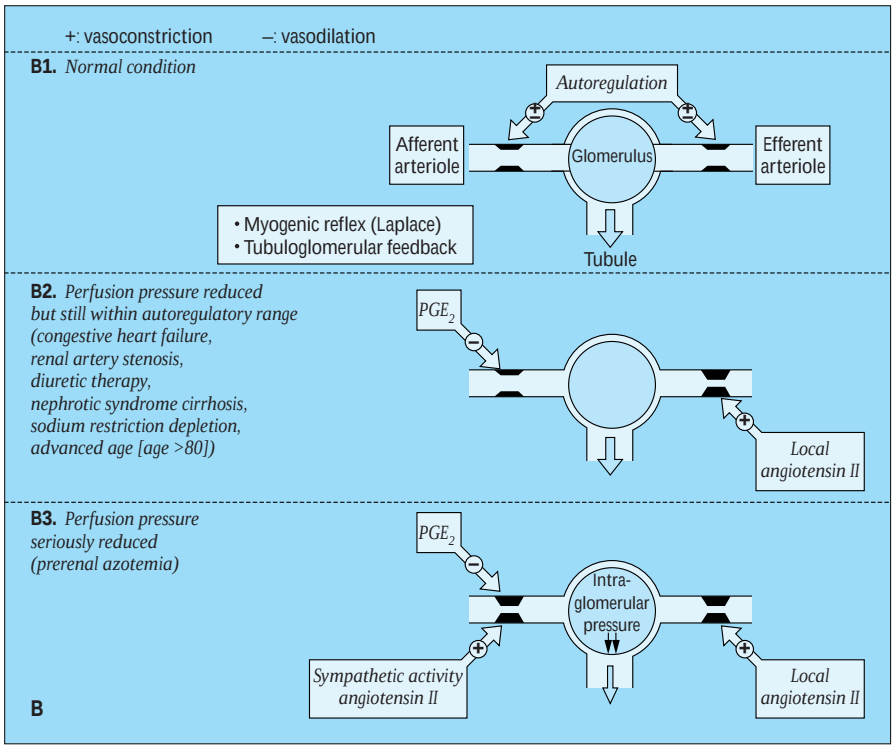

FIGURE 11-16 *(Continued)*

and indirectly via aldosterone. Second, angiotensin II preferentially constricts the efferent arteriole, thus helping to preserve glomerular capillary hydrostatic pressure and, consequently, glomerular filtration rate.

When arterial pressure or body fluid volumes are sensed as subnormal, the renin-angiotensin system is activated and plasma renin activity and angiotensin II levels increase. This may occur in the context of clinical settings such as renal artery stenosis, dietary sodium restriction or sodium depletion as during diuretic therapy, congestive heart failure, cirrhosis, and nephrotic syndrome. When activated, this reninangiotensin system plays an important role in the maintenance of glomerular pressure and filtration through preferential angiotensin II–mediated constriction of the efferent arteriole. Thus, under such conditions the kidney becomes sensitive to the effects of blockade of the renin-angiotensin system by angiotensin I–converting enzyme inhibitor or angiotensin II receptor antagonist.

The highest incidence of renal failure in patients treated with ACE inhibitors was associated with bilateral renovascular disease [27]. In patients with already compromised renal function and congestive heart failure, the incidence of serious changes in serum creatinine during ACE inhibition depends on the severity of the pretreatment heart failure and renal failure.

Volume management, dose reduction, use of relatively short-acting ACE inhibitors, diuretic holiday for some days before initiating treatment, and avoidance of concurrent use of nonsteroidal anti-inflammatory drug (hyperkalemia) are among the appropriate measures for patients at risk.

Acute interstitial nephritis associated with angiotensin I–converting enzyme inhibition has been described [29]. (*Adapted from* Opie [30]; with permission.)

Nonsteroidal Anti-inflammatory Drugs

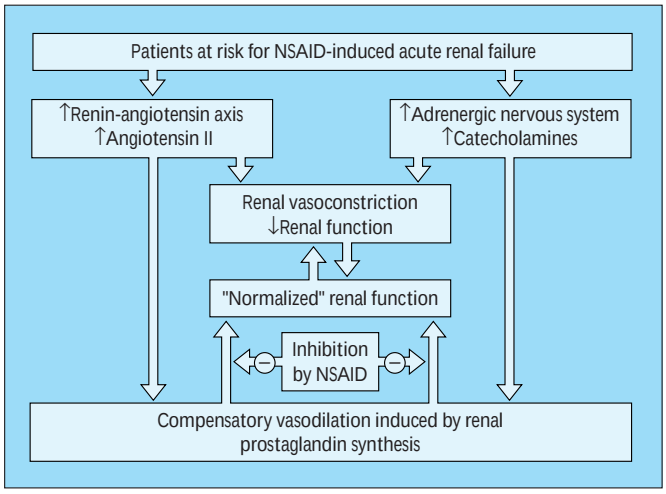

FIGURE 11-17

Mechanism by which nonsteroidal anti-inflammatory drugs (NSAIDs) disrupt the compensatory vasodilatation response of renal prostaglandins to vasoconstrictor hormones in patients with prerenal conditions. Most of the renal abnormalities encountered clinically as a result of NSAIDs can be attributed to the action of these compounds on prostaglandin production in the kidney [31].

Sodium chloride and water retention are the most common side effects of NSAIDs. This should not be considered drug toxicity because it represents a modification of a physiologic control mechanism without the production of a true functional disorder in the kidney.

PREDISPOSING FACTORS FOR NSAID-INDUCED ACUTE RENAL FAILURE

Severe heart disease (congestive heart failure)
Severe liver disease (cirrhosis)
Nephrotic syndrome (low oncotic pressure)
Chronic renal disease
Age 80 years or older
Protracted dehydration (several days)

FIGURE 11-18

Conditions associated with risk for nonsteroidal anti-inflammatory drugs (NSAID)-induced acute renal failure. NSAIDs can induce acute renal decompensation in patients with various renal and extrarenal clinical conditions that cause a decrease in blood perfusion to the kidney [32]. Renal prostaglandins play an important role in the maintenance of homeostasis in these patients, so disruption of counter-regulatory mechanisms can produce clinically important, and even severe, deterioration in renal function.

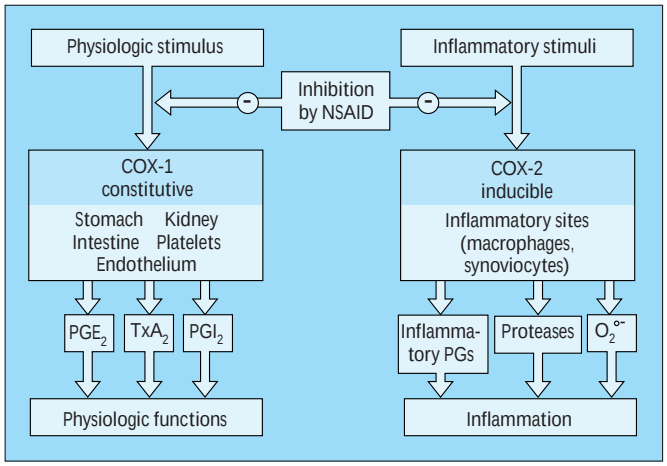

FIGURE11-19

Inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) on pathways of cyclo-oxygenase (COX) and prostaglandin synthesis [33]. The recent demonstration of the existence of functionally distinct isoforms of the cox enzyme has major clinical significance, as it now appears that one form of cox is operative in the gastric mucosa and kidney for prostaglandin generation (COX-1) whereas an inducible and functionally distinct form of cox is operative in the production of prostaglandins in the sites of inflammation and pain (COX-2) [33]. The clinical therapeutic consequence is that an NSAID with inhibitory effects dominantly or exclusively upon the cox isoenzyme induced at a site of inflammation may produce the desired therapeutic effects without the hazards of deleterious effects on the kidneys or gastrointestinal tract. PG—prostaglandin; TxA_2—thromboxane A_2.

EFFECTS OF NSAIDS ON RENAL FUNCTION

Renal Syndrome	Mechanism	Risk Factors	Prevention/Treatment [34]
Sodium retension and edema	↓ Prostaglandin	NSAID therapy (most common side effect)	Stop NSAID
Hyperkalemia	↓ Prostaglandin ↓ Potassium to distal tubule ↓ Aldosterone/renin-angiotensin	Renal disease Heart failure Diabetes Multiple myeloma Potassium therapy Potassium-sparing diuretic	Stop NSAID Avoid use in high-risk patients
Acute deterioration of renal function	↓ Prostaglandin and disruption of hemodynamic balance	Liver disease Renal disease Heart failure Dehydration Old age	Stop NSAID Avoid use in high-risk patients
Nephrotic syndrome with: Interstitial nephritis	↑ Lymphocyte recruitment and activation	Fenoprofen	Stop NSAID Dialysis and steroids (?) Stop NSAID
Papillary necrosis	Direct toxicity	Combination aspirin and acetaminophen abuse	Avoid long-term analgesic use

FIGURE 11-20

Summary of effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on renal function [31].

All NSAIDs can cause another type of renal dysfunction that is associated with various levels of functional impairment and characterized by the nephrotic syndrome together with interstitial nephritis.

Characteristically, the histology of this form of NSAID–induced nephrotic syndrome consists of minimal-change glomerulonephritis with tubulointerstitial nephritis. This is an unusual combination of findings and in the setting of protracted NSAID use is virtually pathognomic of NSAID-related nephrotic syndrome.

A focal diffuse inflammatory infiltrate can be found around the proximal and distal tubules. The infiltrate consists primarily of cytotoxic T lymphocytes but also contains other T cells, some B cells, and plasma cells. Changes in the glomeruli are minimal and resemble those of classic minimal-change glomerulonephritis with marked epithelial foot process fusion.

Hyperkalemia, an unusual complication of NSAIDs, is more likely to occur in patients with pre-existing renal impairment, cardiac failure, diabetes, or multiple myeloma or in those taking potassium supplements, potassium-sparing diuretic therapy, or intercurrent use of an angiotensin-converting enzyme inhibitor. The mechanism of NSAID hyperkalemia—suppression of prostaglandin-mediated renin release—leads to a state of hyporeninemic hypoaldosteronism. In addition, NSAIDs, particularly indomethacin, may have a direct effect on cellular uptake of potassium.

The renal saluretic response to loop diuretics is partially a consequence of intrarenal prostaglandin production. This component of the response to loop diuretics is mediated by an increase in renal medullary blood flow and an attendant reduction in renal concentrating capacity. Thus, concurrent use of an NSAID may blunt the diuresis induced by loop diuretics.

Contrast Medium–Associated Nephrotoxicity

RISK FACTORS THAT PREDISPOSE TO CONTRAST ASSOCIATED NEPHROPATHY

Confirmed	Suspected	Disproved
Chronic renal failure	Hypertension	Myeloma
Diabetic nephropathy	Generalized atherosclerosis	Diabetes without nephropathy
Severe congestive heart failure	Abnormal liver function tests	
Amount and frequency of contrast media	Hyperuricemia	
Volume depletion or hypotension	Proteinuria	

FIGURE 11-21

Risk factors that predispose to contrast-associated nephropathy. In random populations undergoing radiocontrast imaging the incidence of contrasts associated nephropathy defined by a change in serum creatinine of more than 0.5 mg/dL or a greater than 50% increase over baseline, is between 2% and 7%. For confirmed high-risk patients (baseline serum creatinine values greater than 1.5 mg/dL) it rises to 10% to 35%. In addition, there are suspected risk factors that should be taken into consideration when considering the value of contrast-enhanced imaging.

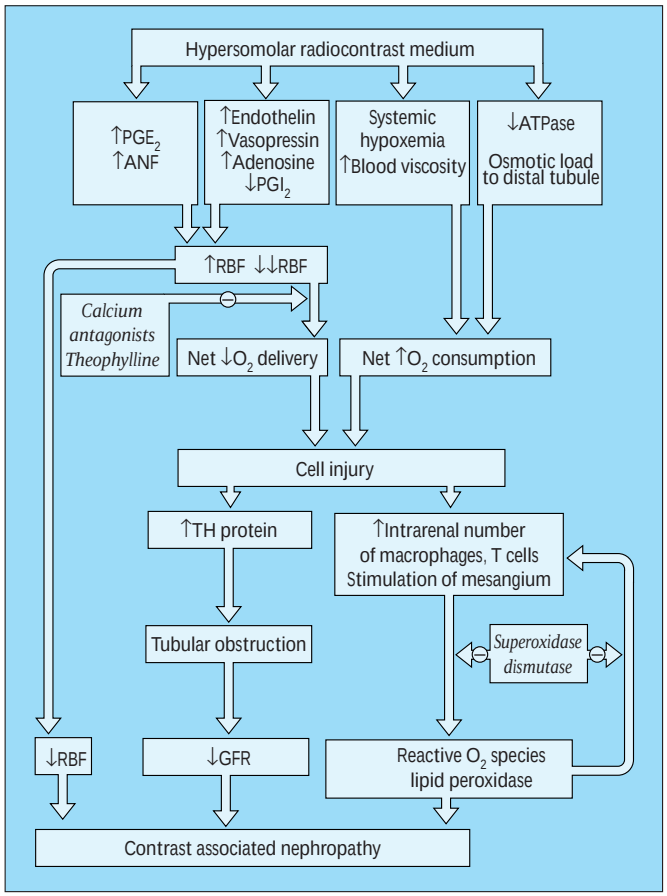

FIGURE 11-22

A proposed model of the mechanisms involved in radiocontrast medium–induced renal dysfunction. Based on experimental models, a consensus is developing to the effect that contrast-associated nephropathy involves combined toxic and hypoxic insults to the kidney [35]. The initial glomerular vasoconstriction that follows the injection of radiocontrast medium induces the liberation of both vasoconstrictor (endothelin, vasopressin) and vasodilator (prostaglandin E_2 [PGE_2], adenosine, atrionatiuretic factor {ANP}) substances. The net effect is reduced oxygen delivery to tubule cells, especially those in the thick ascending limb of Henle. Because of the systemic hypoxemia, raised blood viscosity, inhibition of sodium-potassium–activated ATPase and the increased osmotic load to the distal tubule at a time of reduced oxygen delivery, the demand for oxygen increases, resulting in cellular hypoxia and, eventually cell death. Additional factors that contribute to the acute renal dysfunction of contrast-associated nephropathy are the tubule obstruction that results from increased secretion of Tamm-Horsfall proteins and the liberation of reactive oxygen species and lipid peroxidation that accompany cell death. As noted in the figure, calcium antagonists and theophylline (adenosine receptor antagonist) are thought to act to diminish the degree of vasoconstriction induced by contrast medium.

The clinical presentation of contrast-associated nephropathy involves an asymptomatic increase in serum creatinine within 24 hours of a radiographic imaging study using contrast medium, with or without oliguria [36].

We have recently reviewed the clinical outcome of 281 patients with contrast-associated nephropathy according to the presence or absence of oliguric acute renal failure at the time of diagnosis. Of oliguric acute renal failure patients, 32% have persistent elevations of serum creatinine at recovery and half require permanent dialysis. In the absence of oliguric acute renal failure the serum creatinine value does not return to baseline in 24% of patients, approximately a third of whom require permanent dialysis. Thus, this is not a benign condition but rather one whose defined risks are not only permanent dialysis but also death. GFR—glomerular filtration rate; RBF—renal blood flow; TH—Tamm Horsfall protein.

PREVENTION OF CONTRAST ASSOCIATED NEPHROPATHY

Hydrate patient before the study (1.5 mL/kg/h) 12 h before and after.
Hemodynamically stabilize hemodynamics.
Minimize amount of contrast medium administered.
Use nonionic, iso-osmolar contrast media for patients at high risk (*see* Figure 11-21).

FIGURE 11-23

Prevention of contrast-associated nephropathy. The goal of management is the prevention of contrast-associated nephropathy.

Thus it is important to select the least invasive diagnostic procedure that provides the most information, so that the patient can make an informed choice from the available clinical alternatives.

Since radiographic contrast imaging is frequently performed for diabetic nephropathy, congestive heart failure, or chronic renal failure, concurrent administration of renoprotective agents has become an important aspect of imaging. A list of maneuvers that minimize the risk of contrast-associated nephropathy is contained in this table. The correction of prestudy volume depletion and the use of active hydration before and during the procedure are crucial to minimizing the risk of contrast-associated nephropathy. Limiting the total volume of contrast medium and using nonionic, isoosmolar media have proven to be protective for high-risk patients. Pretreatment with calcium antagonists is an intriguing but unsubstantiated approach.

References

1. Bennett WM, Porter GA: Overview of clinical nephrotoxicity. In *Toxicology of the Kidney*, edn 2. Edited by Hook JB, Goldstein RS. Raven Press, 1993:61–97.
2. Thadhani R, Pascual M, Bonventre JV: Acute renal failure. *N Engl J Med* 1996, 334:1448–1460.
3. De Broe ME: Prevention of aminoglycoside nephrotoxicity. In *Proc EDTA-ERA*. Edited by Davison AM, Guillou PJ. London:BailliËre Tindal, 1985:959–973.
4. Lietman PS: Aminoglycosides and spectinoycin: aminocylitols. In *Principles and Practice of Infectious Diseases*, edn 2, Part I. Edited by Mandel GL, Doublas RG Jr, Bennett JE. New York: John Wiley & Sons, 1985:192–206.
5. Kaloyanides GJ, Pastoriza-Munoz E: Aminoglycoside nephrotoxicity. *Kidney Int* 1980, 18:571–582.
6. Molitoris BA. Cell biology of aminoglycoside nephrotoxicity: newer aspects. *Curr Opin Nephrol Hypertens* 1997, 6:384–388.
7. De Broe ME, Paulus GJ, Verpooten GA, *et al.*: Early effects of gentamicin, tobramycin, and amikacin on the human kidney. *Kidney Int* 1984, 25:643–652.
8. Giuliano RA, Verpooten GA, Verbist L, *et al.*: In vivo uptake kinetics of aminoglycosides in the kidney cortex of rats. *J Pharmacol Exp Ther* 1986, 236:470–475.
9. Giuliano RA, Verpooten GA, De Broe ME: The effect of dosing strategy on kidney cortical accumulation of aminoglycosides in rats. *Am J Kidney Dis* 1986, 8:297–303.
10. Verpooten GA, Giuliano RA, Verbist L, *et al.*: A once-daily dosage schedule decreases the accumulation of gentamicin and netilmicin in the renal cortex of humans. *Clin Pharmacol Ther* 1989, 44:1–5.
11. De Broe ME, Verbist L, Verpooten GA: Influence of dosage schedule on renal cortical accumulation of amikacin and tobramycin in man. *J Antimicrob Chemother* 1991, 27 (suppl C):41–47.
12. Bennett WM, Plamp CE, Gilbert DN, *et al.*: The influence of dosage regimen on experimental gentamicin nephrotoxicity: dissociation of peak serum levels from renal failure. *J Infect Dis* 1979, 140:576–580.
13. Moore RD, Smith CR, Lipsky JJ, *et al.*: Risk factors for nephrotoxicity in patients treated with aminoglycosides. *Ann Intern Med* 1984, 100:352–357.
14. Zager RA: A focus of tissue necrosis increases renal susceptibility to gentamicin administration. *Kidney Int* 1988; 33:84–90.
15. Andreoli TE: On the anatomy of amphotericin B-cholesterol pores in lipid bilayer membranes. *Kidney Int* 1973, 4:337–45.
16. Bernardo J, Sabra R, Branch RA: Amphotericin B. In *Clinical Nephrotoxins—Renal Injury From Drugs and Chemicals*. Edited by De Broe ME, Porter GA, Bennett WM, Verpooten GA. Dordrecht: Kluwer Academic, 1998:135–151.
17. Bennett WM: Mechanisms of acute and chronic nephrotoxicity from immunosuppressive drugs. *Renal Failure* 1996, 18:453–460.
18. de Mattos AM, Olyaei AJ, Bennett WM: Pharmacology of immunosuppressive medications used in renal diseases and transplantation. *Am J Kidney Dis* 1996, 28:631–667.
19. Vanrenterghem Y, Lerut T, Roels L, *et al.*: Thromboembolic complications and haemostatic changes in cyclosporin-treated cadaveric kidney allograft recipients. *Lancet* 1985, 1:999–1002.
20. Verpooten GA, Cools FJ, Van der Planken MG, *et al.*: Elevated plasminogen activator inhibitor levels in cyclosporin-treated renal allograft recipients. *Nephrol Dial Transplant* 1996, 11:347–351.
21. Vestergaard P, Amdisen A, Hansen AE, Schou M: Lithium treatment and kidney function. *Acta Psychiatry Scand* 1979; 60:504–520.
22. Johnson GF, Hunt G, Duggin GG, *et al.*: Renal function and lithium treatment: initial and follow-up tests in manic-depressive patients. *J Affective Disord* 1984; 6:249–263.
23. Coppen A, Bishop ME, Bailey JE, *et al.*: Renal function in lithium and non–lithium-treated patients with affective disorders. *Acta Psychiatry Scand* 1980; 62:343–355.
24. Battle DC, Dorhout-Mees EJ: Lithium and the kidney. In *Clinical nephrotoxins—renal injury from drugs and chemicals*. Edited by De Broe ME, Porter GA, Bennett WM, Verpooten GA. Dordrecht: Kluwer Academic, 1998:383–395.
25. Jorgensen F, Larsen S, Spanager E, *et al.*: Kidney function and quantitative histological changes in patients on long-term lithium therapy. *Acta Psychiatry Scand* 1984, 70:455–462.
26. Hricik DE, Browning PJ, Kopelman R, *et al.*: Captopril-induced functional renal insufficiency in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. *N Engl J Med* 1983, 308:373–376.
27. Textor SC: ACE inhibitors in renovascular hypertension. *Cardiovasc Drugs Ther* 1990; 4:229–235.
28. de Jong PE, Woods LL: Renal injury from angiotensin I converting enzyme inhibitors. In *Clinical nephrotoxins—renal injury from drugs and chemicals*. Edited by De Broe ME, Porter GA, Bennett WM, Verpooten GA. Dordrecht: Kluwer Academic, 1998:239–250.
29. Smith WR, Neil J, Cusham WC, Butkus DE: Captopril associated acute interstitial nephritis. *Am J Nephrol* 1989, 9:230–235.
30. Opie LH: *Angiotensin-converting enzyme inhibitors*. New York: Willy-Liss, 1992; 3.
31. Whelton A, Watson J: Nonsteroidal anti-inflammatory drugs: effects on kidney function. In *Clinical Nephrotoxins—Renal Injury From drugs and Chemicals*. Edited by De Broe ME, Porter GA, Bennett WM, Verpooten GA. Dordrecht: Kluwer Academic, 1998:203–216.
32. De Broe ME, Elseviers MM: Analgesic nephropathy. *N Engl J Med* 1998, 338:446–452.
33. Mitchell JA, Akarasereenont P, Thiemermann C, *et al.*: Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci USA* 1993, 90(24):11693–11697.
34. Bennett WM, Henrich WL, Stoff JS: The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. *Am J Kidney Dis* 1996, 28(1 Suppl 1):S56–S62.
35. Heyman SN, Rosen S, Brezis M: Radiocontrast nephropathy: a paradigm for the synergism between toxic and hypoxic insults in the kidney. *Exp Nephrol* 1994, 2:153.
36. Porter GA, Kremer D: Contrast associated nephropathy: presentation, pathophysiology and management. In *Clinical nephrotoxins—Renal Injury From Drugs and Chemicals*. Edited by De Broe ME, Porter GA, Bennett WM, Verpooten GA. Dordrecht: Kluwer Academic, 1998:317–331.